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A Novel Reduced-Intensity Conditioning Regimen Induces a High Incidence of Sustained Donor-Derived Neutrophil and Platelet Engraftment after Double-Unit Cord Blood Transplantation

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A B S T R A C T

A preparative regimen of reduced intensity that can reliably engraft cord blood (CB) and can be used as an alternative to either high-dose myeloablative or nonmyeloablative conditioning is needed. We evaluated double-unit CB transplantation in 30 patients (median age, 56 years; range, 18 to 69) with acute leukemia or myelodysplasia using a regimen of cyclophosphamide 50 mg/kg, fludarabine 150 mg/m^2, thiotepa 10 mg/kg, and 400 cGy total body irradiation with cyclosporine-A/mycophenolate mofetil immunosuppression. Ninety-seven percent of patients engrafted at a median of 26 days (range, 13 to 43), and 93% of patients had recovered platelets by day 180. Grades II to IV acute graft-versus-host disease (GVHD) incidence was 67% at day 180, and chronic GVHD was 10% at 1 year. Transplant-related mortality was 20% at day 180, and relapse was 11% at 2 years. Overall, 2-year disease-free survival (DFS) was 60% at 2 years. A hierarchy in DFS was seen according to the Sorror comorbidity score: 11 patients (median age, 55 years) with a score of 1 had a 2-year DFS of 82% compared with 62% in 9 patients (median age, 51 years) with a score of 2 to 3 and 40% in 11 patients (median age, 58 years) with a score of 4 to 5 ($P = .13$). This reduced-intensity regimen combined with double-unit CB transplantation reliably facilitates sustained donor engraftment without antithymocyte globulin. Although other approaches are needed in patients with high comorbidity scores, this regimen is highly effective in patients ≥50 years old who are otherwise reasonably fit. It also represents a promising alternative to high-dose conditioning in younger patients.

INTRODUCTION

Double-unit cord blood transplantation (CBT) has been effective at reducing transplant-related mortality (TRM) compared with single-unit CBT historical control subjects [1]. Improvement in high-dose myeloablative double-unit CBT is needed, however, due to the risk of lethal regimen-related organ toxicity [2]. Nonmyeloablative (NMA) and reduced-intensity conditioning have been investigated as strategies to reduce TRM and extend transplant access to older patients or those with significant comorbidities [3-6]. However, NMA conditioning is limited by the combined risks of graft rejection in patients without extensive prior chemotherapy [3] and relapse [7-9]. Although rejection may be reduced by adding antithymocyte globulin (ATG), this in vivo T cell depletion increases the risk of viral infections and Epstein-Barr virus lymphoproliferative disease [10,11] and has been associated with increased TRM [4]. ATG could also increase relapse risk [12,13].

To address these limitations, we investigated the safety and efficacy of a novel ATG-free reduced-intensity regimen. We used the cyclophosphamide, fludarabine, total body irradiation (TBI) 200 cGy NMA platform originally reported by the University of Minnesota [3,4], but we intensified the regimen by adding thiotepa and increasing the TBI dose to 400 cGy. In addition, to augment engraftment and possibly the antileukemia potential [14-17], we used double-unit grafts in all patients. We investigated this double-unit CBT approach as an alternative to either high-dose myeloablative or NMA conditioning in adult patients with the hypothesis that it would induce a high incidence of sustained donor engraftment without ATG and have a low incidence of relapse.

METHODS

Patients Characteristics

Patients underwent transplantation at Memorial Sloan-Kettering Cancer Center between October 1, 2007 and August 30, 2011, and provided informed consent for transplantation and outcome analysis in accordance with the Declaration of Helsinki. The trial is registered on ClinicalTrials.gov (NCT00739141). We report in this analysis all consecutive patients age 18 to 69 years who first received hematopoietic stem cell transplants and with diagnoses of acute myelogenous or lymphoblastic leukemia in complete morphologic remission (CR1 to CR3) or myelodysplasia with ≤5% blasts. The indication for this reduced-intensity regimen was a diagnosis of acute

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leukemia or myelodysplastic syndrome (MDS) and 1 or more TRM risk factors of age ≥50 years, and/or extensive prior therapy, and/or significant comorbidities, making the patient ineligible or inappropriate for high-dose myeloablative conditioning. Standard-risk disease for acute leukemia was defined as CR1 without high-risk cytogenetics/high-risk molecular abnormalities or de novo myelodysplasia with an International Prognostic Scoring System score <2. All remaining patients were considered high risk [2]. The hematopoietic cell transplant comorbidity index (HCT-CI) score of Sorror et al. [18] was retrospectively assigned for the purposes of this analysis.

Conditioning Regimen, Graft-versus-Host Disease Prophylaxis, and Graft Characteristics

Conditioning consisted of cyclophosphamide 50 mg/kg (day −6), fludarabine 30 mg/m^2/day for 5 (days −6 to −2), thiotepa 5 mg/kg/day for 2 (days −5 and −4), and TBI 200 cGy/day for 2 (days −2 and −1) (Cy 50/Flu 150/Thio 10/TBI 400). If the recipient was greater than 125% of ideal body weight, the doses of cyclophosphamide, fludarabine, and thiotepa were calculated on adjusted body weight.

Cyclosporine A and mycophenolate mofetil were used as graft-versus-host disease (GVHD) prophylaxis starting on day −3 intravenously. Cyclosporine A was dosed to achieve a trough level of 200 to 400 ng/mL. Mycophenolate mofetil was given in a dose of 1 g every 12 hours for the first 17 patients and was increased to 1 g every 8 hours for the subsequent 13 patients to augment GVHD prophylaxis [19].

Double-unit CB grafts were 4-6/6 human leukocyte antigen (HLA)-A, -B antigen, -DRB1 allele matched to the recipient with a cryopreserved total nucleated cell dose ≥1.5 × 10^7/kg/unit as previously described [20]. Unit-to-unit HLA match was not considered in unit selection. Units were thawed with albumin-dextran dilution [21] (n = 58) or were washed (n = 2). Granulocyte colony-stimulating factor (5 μg/kg/day rounded to vial size) was given from day 7 until neutrophil recovery.

Study Definitions

Time to neutrophil recovery was defined as the first of 3 consecutive days with an absolute neutrophil count >.5 × 10^9/L. Time to platelet recovery was defined as the first of 3 consecutive days at >50 × 10^9/L and at least 7 days without platelet transfusion support. Sustained donor engraftment was defined as sustained donor-derived count recovery with donor chimerism of at least 90% (both units combined). GVHD was diagnosed clinically with histologic confirmation when appropriate. Acute and chronic GVHD were graded according to the International Bone Marrow Transplant Registry [22] and the National Institutes of Health consensus criteria [23], respectively.

The primary aim of this study was to obtain a preliminary estimate of disease-free survival (DFS) at 1 year after CBT. The target sample size was 30 patients. We proposed the treatment would be considered efficacious if the DFS at 1 year was at least 50%. Using a single-stage design, if at least 19 of 30 patients were disease-free at 1 year, there would be a 90% confidence that the true 1-year DFS of >50%. Overall survival and DFS rates were calculated using Kaplan-Meier methodology, and cumulative incidence was used to estimate all other outcomes. The permutation log-rank test was used to test for differences in DFS according to HCT-CI score.

RESULTS

Patient and Graft Characteristics

Table 1 summarizes patient and graft characteristics. Thirty patients (median age, 56 years) underwent transplantation. Twenty-six had acute leukemia (20 CR1, 5 CR2, 1 CR3), and 4 had MDS. All had high-risk disease (as described in Table 1), except a single patient who had refractory anemia with excess blasts −2 that achieved CR after treatment. All patients had been treated with either chemotherapy (n = 28) or hypomethylating agents (n = 2). Twenty-seven patients had received therapy within the preceding 3 months, and 3 patients were treated >3 months before transplantation.

The median HCT-CI score [18] was 2.5 (range, 1 to 5). The age distribution of patients with HCT-CI scores of 1 (n = 11; median, 55 years; range, 31 to 66), 2 to 3 (n = 9; median, 51 years; range, 35 to 61), and 4 to 5 (n = 10; median, 58 years; range, 18 to 69) was not different (P = .84). Comorbidities as defined by Sorror et al. [18] included arrhythmia (n = 1), cardiovascular disease (n = 4), diabetes (n = 2), depression/anxiety (n = 1), hepatic dysfunction (n = 7, all mild), infection requiring ongoing therapy (n = 5), pulmonary dysfunction (n = 15, 9 moderate and 6 severe), and prior solid tumor (n = 4) [13].

Table 1
Patient (n = 30) and Graft Characteristics (60 units)

Characteristics	Value
Median age, yr (range)	56 (18-69)
Male, n (%)	15 (50)
Median weight, kg (range)	69 (48-103)
Recipient CMV seropositive, n (%)	21 (70)
Diagnosis/disease status,* n (%)	
AML	21 (70)
CR1	16
3 poor risk cytogenetics†	
5 FLT3-ITD mutation	
6 secondary to therapy or prior MDS/MPD	
2 with ≥3 inductions	
CR2	5
ALL	5 (17)
CR1	4
3 Philadelphia chromosome-positive	
1 refractory CNS disease that cleared before allograft	
CR3	1
MDS	4 (13)
CR1	1
Stable disease	1
Hematologic improvement	2
Disease risk, n (%)	
Standard	1 (3)
High	29 (97)
Donor–recipient HLA-match, n (%)	
6/6	4 (7)
5/6	32 (53)
4/6	24 (40)
Median infused TNC × 10^7/kg (range)	
Larger unit	2.6 (1.5-5.6)
Smaller unit	1.9 (1.4-2.5)
Median infused CD34+ × 10^5/kg (range)	
Larger unit	.9 (.4-3.3)
Smaller unit	.5 (.2-1.5)

CMV indicates cytomegalovirus; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MPD, myeloproliferative disease; TNC, total nucleated cell.

* Two patients had multiple hematologic malignancies: 1 with AML and chronic lymphocytic leukemia and 1 with MDS and non-Hodgkin lymphoma.

† Included monosomy 7 (n = 1), 11q23 translocation (n = 1), and del 5q (n = 1).

Regimen-Related Toxicity, Engraftment, GVHD, and Infections

The regimen was associated with delayed engraftment characteristic of myeloablative regimens. Although it was better tolerated than high-dose chemoradiation, there were high rates of anorexia, with 21 of 30 patients (70%) requiring total parenteral nutrition. However, mucositis was not severe, and only 8 needed patient-controlled analgesia with narcotics within the first 4 weeks posttransplantation. Three patients suffered organ toxicity, resulting in TRM as described below. The only late toxicities were associated with GVHD and its treatment.

Ninety-seven percent (95% confidence interval [CI], 87 to 100) of patients had sustained donor-derived neutrophil engraftment (Figure 1). The median time to neutrophil recovery was 26 days (range, 13 to 43). A single, heavily pretreated patient had graft failure in the context of early-onset multiorgan failure. The patient's bone marrow was 100% donor 21 days after transplantation. However, the patient died 35 days after transplantation without count recovery. The cumulative incidence of platelet recovery of

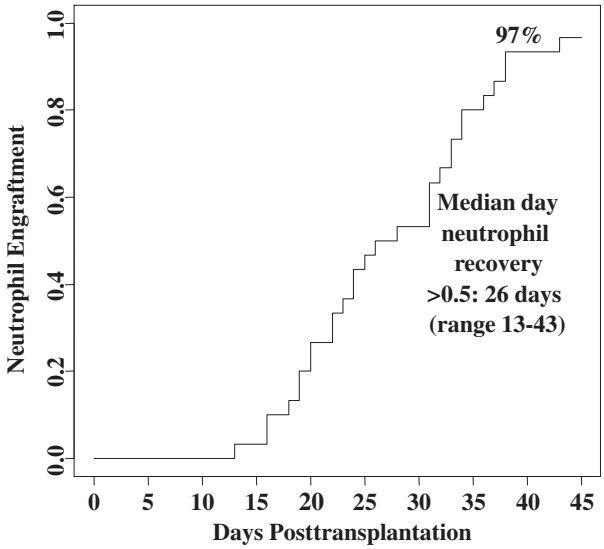

Figure 1. Cumulative incidence of neutrophil engraftment.

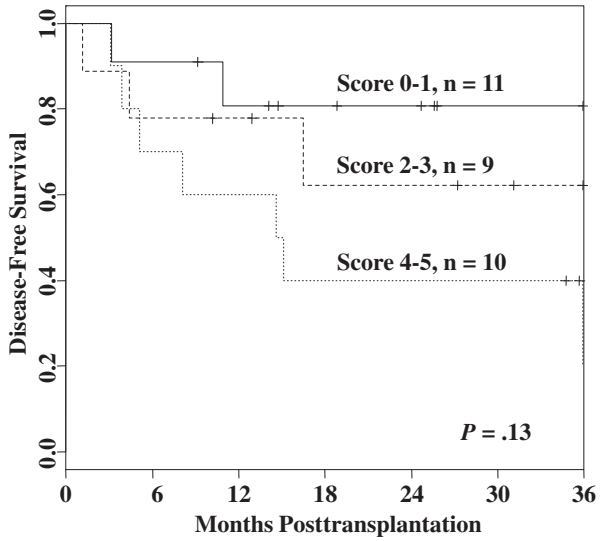

Figure 3. DFS according to the HCT-CI after double-unit CBT using Cy 50/Flu 150/Thio 10/TBI 400 conditioning.

20×10^9/L by day 180 was 93% (95% CI, 83 to 100) and occurred at a median of 46 days (range, 30 to 79). The median day 21 total donor bone marrow chimerism was 100% (range, 71 to 100) and consisted of 1 unit in 25 of 30 patients (83%). All surviving patients were 100% donor at 100 days after transplantation, there were no late graft failures, and sustained hematopoiesis has been mediated by a single unit in all but 1 patient.

Sixty-seven percent (95% CI, 49 to 84) of patients had grades II to IV and 7% (95% CI, 0 to 16) had grades III to IV acute GVHD by day 180 (17 grade II, 2 grade III, and 1 grade IV). Of the 27 patients who engrafted and were alive at day 100, 3 had chronic GVHD (2 overlap and 1 classical; 2 mild and 1 moderate severity). The 1-year cumulative incidence of chronic GVHD was 10% (95% CI, 0 to 21).

The pattern of infectious complications was similar to that previously described in recipients of double-unit CBT transplanted without ATG [24]. Eighteen of the 21 patients (86%) who were cytomegalovirus seropositive reactivated cytomegalovirus at a median of 43 days (range, 14 to 111) posttransplantation. However, only 2 had end-organ disease (both with gastrointestinal involvement, 1 in the setting of GVHD). Two patients had Epstein-Barr virus viremia at +5 and + 21 months posttransplantation, both in the setting of treatment for GVHD. Both responded to rituximab therapy, and no patient had Epstein-Barr virus lymphoma.

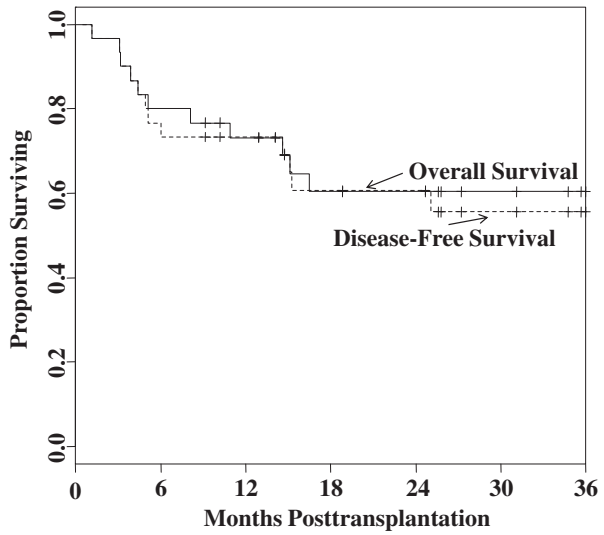

Figure 2. Kaplan-Meier estimate of overall survival and DFS.

TRM, Relapse, and Survival

TRM was 20% (95% CI, 5 to 35) at day 180 and 28% (95% CI, 11 to 46) at 2 years. Of 8 patients who died of transplant-related causes, 1 died of graft failure, 4 of GVHD, and 3 of organ failure (2 pulmonary, 1 central nervous system). No patient died of infection as the primary cause of death. Relapse was 11% (95% CI, 3 to 26) at 2 years. With a median 26.5-month (range, 9 to 53) follow-up of survivors, the 2-year overall survival and DFS were both 60% (95% CI, 44 to 82) (Figure 2).

The comparison of DFS according to pretransplantation HCT-CI is shown in Figure 3. In the 11 patients (median age, 55 years) with an HCT-CI score of 1, 1 has died of transplant-related causes and 1 has relapsed, resulting in a 2-year DFS of 82% (95% CI, 62 to 100) in this group. This compares favorably with the 2-year DFS of 62% (95% CI, 36 to 100) in 9 patients (median age, 51 years) with a score of 2 to 3 (2 cases of TRM and 1 relapse), and the 2-year DFS of 40% (95% CI, 44 to 82) in 10 patients (median age, 58 years) with a score of 4 to 5 (5 cases of TRM and 2 relapses) (permutation log-rank $P = .13$).

DISCUSSION

We demonstrate that Cy 50/Flu 150/Thio 10/TBI 400 conditioning supports a high incidence of sustained neutrophil and platelet engraftment after double-unit CBT. This regimen is reduced intensity based on the lower doses of chemotherapy and TBI than are delivered in high-dose regimens and as defined by the criteria of Bacigalupo et al. [25]. However, it remains functionally myeloablative as illustrated by the delayed neutrophil recovery characteristic of adult CBT and the median day 21 total donor chimerism of 100%. This is in contrast to the transient autologous recovery and initial mixed chimerism characteristic of NMA double-unit CBT [3]. Other centers have investigated CBT with

reduced-intensity regimens in an effort to avoid the toxicity of the most intense regimens. These include melphalan/fludarabine [5], melphalan/thiotepa/fludarabine [26], and treosulfan/fludarabine/TBI [27].

The Cy 50/Flu 150/Thio 10/TBI 400 regimen induces sufficient immunosuppression to facilitate sustained donor engraftment when combined with a double-unit CB graft, and this is achieved without the profound posttransplantation immunosuppression associated with ATG. It should be acknowledged, however, that our series did not contain any patient without prior therapy, although 2 patients had received only hypomethylating agents. Patients without prior combination chemotherapy (who are at an increased risk of graft rejection after NMA CBT [3]) require further investigation. Furthermore, although the incidence rates of both neutrophil and platelet engraftment were high, the rate of recovery is quite delayed relative to the transplantation of adult donor peripheral blood stem cells. New strategies, such as a larger CB inventory to enable transplantation of larger and better matched units, ex vivo expansion [28,29], or the addition of a T cell–depleted haploidentical graft [30,31], could further improve the rate of count recovery after this regimen. In addition, although we found a high incidence of acute GVHD, most cases were not severe. Whether the increase in mycophenolate mofetil dosing will afford more effective GVHD prophylaxis requires analysis of larger patient numbers. It is likely, however, that new agents will be needed to augment GVHD prevention without the disadvantages of ATG. As previously described by our group, in the absence of ATG, late infection risk was low in the absence of moderate to severe GVHD [24].

The pretransplantation HCT-CI of Sorror et al. has been validated as a reliable tool to predict allograft TRM and survival based on recipient pretransplantation comorbidities (significant prior illnesses and organ dysfunction) [24]. The utility of the HCT-CI has recently been demonstrated in a large prospective study [32]. Notably, in our much smaller double-unit CBT series, an association between HCT-CI and DFS is also suggested. The low TRM affecting only 1 of 11 patients with a score of 1 is notable, given their relatively advanced median age of 55 years by CBT standards. Thus, Cy 50/Flu 150/Thio 10/TBI 400 double-unit CBT can be safely used in patients $\geq$50 years old without other major TRM risks. Although the upper age limit for safe administration of this regimen is not known, our findings are highly significant for middle-age patients with high-risk acute leukemias who are otherwise fit and suggests that double-unit CBT with Cy 50/Flu 150/Thio 10/TBI 400 could be an immediate alternative if an unrelated donor is not identified within the first few weeks of a search. In contrast, TRM risk for patients with a high HCT-CI score ($\geq$4) remains substantial with this regimen. Unfortunately, high comorbidity scores cannot be modified. Although earlier referral of patients with high-risk disease could reduce the impact of prior therapy, our data suggest this regimen remains too intense for such patients, and other treatmentation approaches are needed. These could include nontransplantation therapies or the investigation of NMA allografts with posttransplantation maintenance to reduce relapse risk as has been investigated for patients with acute myelogenous leukemia and MDS [33].

Unlike NMA conditioning, which has been associated with a 31% relapse incidence at 1-year follow-up [8], the incidence of leukemic relapse in this high-risk population has been low (11% at 2 years with a median follow-up of 26.5 months). The combined effects of this conditioning and the graft-versus-leukemia potential of double-unit grafts [14-17] may well account for this outcome.

It should be acknowledged that this series is relatively small. Nonetheless, our promising preliminary results warrant further investigation in patients age $\geq$50 years with high-risk hematologic malignancies, who have high relapse risks after NMA conditioning and acceptable comorbidity scores. It may also be a promising alternative to high-dose conditioning in younger patients with hematologic malignancies, due to the reduced organ toxicity and preservation of the protection against relapse. As a result, we are now prioritizing this approach for most of our adult patients undergoing double-unit CBT, even those previously considered eligible for high-dose conditioning.

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